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Treatments for subacute cough in primary care:

systematic review and meta-analyses of randomised clinical trials

Abstract

Background
Subacute cough following a non-specific viral infection lasting 3–8 weeks is common. However, despite many treatment options there are no systematic reviews evaluating these.

Aim
To provide a systematic overview of treatment options and outcomes evaluated in randomised clinical trials (RCTs).

Design and setting
Systematic review and meta-analyses assessing the overall effects of any treatment for subacute cough.

Method
The authors systematically searched PubMed/MEDLINE and the Cochrane Central Register of Controlled Trials (last search March 2017) for RCTs in adult patients with subacute cough. The authors considered trials evaluating any outcome of any drug or non-drug treatments, apart from traditional Chinese and Asian medicines. They combined treatment effects on cough-related outcomes in random effects meta-analyses.

Results
Six eligible RCTs including 724 patients were identified. These assessed montelukast, salbutamol plus ipratropium bromide, gelatine, fluticasone propionate, budesonide, and nociception opioid 1 receptor agonist and codeine. Five studies reported effects on various cough severity scores at various timepoints. No treatment option was associated with a clear benefit on cough recovery or other patient-relevant outcomes in any of the studies or in meta-analyses for cough outcomes at 14 days and 28 days. Reported adverse events were rather mild and reported for 14% of patients across all treatments.

Conclusion
Evidence on treatment options for subacute cough is weak. There is no treatment showing clear patient-relevant benefits in clinical trials.

Keywords
cough; cough score; disease progression; subacute; treatment.

INTRODUCTION

Cough is one of the most common reasons for seeking medical advice in primary care.[1] Prolonged cough following an upper respiratory tract infection may substantially affect quality of life and psychosocial wellbeing.[2] Patients may seek medical advice for several reasons, including frustration, irritability, anger, and sleep disturbances, as well as anxiety about an underlying serious illness such as cancer.[3] Treatment strategies for patients with prolonged cough are challenging, and the question of whether or not to prescribe antibiotics also frequently arises. Antibiotics are not recommended for the treatment of prolonged cough symptoms.[4] Although GPs are aware of this, they may feel that their patients urge them to prescribe antibiotics.[5] Cough can also have a socioeconomic impact due to the number of consultations and related costs, absence from work, and over-the-counter drug prescriptions.[6–9] It is estimated $4 billion is spent worldwide on antitussive drugs per year.[8] In the UK, the economic burden is estimated to be at least £979 million per year, comprising of £875 million in lost productivity and £104 million in costs to the healthcare system.[9]

In general, cough can be acute (lasting <3 weeks), subacute (3–8 weeks of symptoms), or chronic (symptoms last >8 weeks).[10,11] Although chronic cough is most commonly caused by asthma and gastroesophageal reflux disease (GORD), or occurs within an upper airway cough syndrome,[12] subacute cough often follows non-specific viral infections causing protracted inflammation of the bronchial mucosa and extensive disruption of epithelial integrity without chronic underlying conditions.[4,13,14] The American College of Chest Physicians (ACCP) defines subacute cough as cough that: *'... lasts no* [longer than] *8 weeks; the chest radiography findings are negative ruling out pneumonia; and the cough eventually resolves, usually on its own'*.[4] Diagnosis is based on medical history and physical examination excluding other underlying causes, such as asthma or GORD.[4,15] Although subacute cough usually improves spontaneously without treatment,[10] a variety of treatments are proposed for alleviation, some of which have been assessed in systematic reviews focusing on very selected drug interventions.[16–18] However, no systematic review has evaluated all treatment options.

The authors conducted a systematic review and meta-analysis of randomised clinical trials (RCTs) to provide a wide overview of patient-relevant benefits and harms of available treatments.

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How this fits in

Cough after a respiratory infection is one of the most common reasons for seeking medical advice. Despite a large number of available treatment options for subacute cough there has been no systematic review evaluating these treatments. The authors systematically searched for randomised clinical trials assessing treatment effects and found that the evidence on the large variety of treatment options for subacute cough is weak.

METHOD

Search strategy and inclusion criteria

An information specialist searched MEDLINE via PubMed (from inception until 10 February 2017) and the Cochrane Central Register of Controlled Trials (CENTRAL; from inception until 16 March 2017) for RCTs and systematic reviews of RCTs using standard filters[19] without language restrictions (further details are available from author on request).

The authors included RCTs in patients aged ≥16 years with a cough of 3–8 weeks (that is, subacute) and without known chronic respiratory diseases or other related diagnoses with overlapping symptoms (for example, GORD, chronic obstructive pulmonary disease [COPD], or asthma). The authors also included trials with slightly shorter or longer cough duration (that is, a minimum of 2 weeks, a maximum of 10 weeks) or with a less specific definition (that is, no maximum duration reported; for example, '>2 weeks') to evaluate further potentially pertinent evidence, given the rather arbitrary cut-off-definition of subacute. Any reported health outcomes, including any adverse events, were evaluated.

The authors considered any drug or non-drug treatment, including traditional Western cough remedies or medicines, herbal or other natural products, and preparations with minimal processing from the European–North American region.[20–22] They did not consider Chinese or Asian herbal medicine.[23] A valid and unbiased assessment of such interventions would require a thorough search and evaluation of the Chinese and Asian literature, which was beyond the scope of this project. The authors included studies published in English, German, Italian, Spanish, or French. No further eligibility criteria were applied.

The authors hand searched reference lists of included trials, pertinent systematic reviews, and selected current clinical guidelines of primary care,[4,15] and screened all citations of pertinent trials using SCOPUS (9 August 2017) to identify potentially relevant RCTs.

Two reviewers independently screened titles and abstracts, and conducted the hand searching and citation screening. Any potentially relevant full text was obtained to determine eligibility. Disagreements were resolved by discussion, or with a third reviewer.

Data extraction and risk of bias assessment

From included RCTs the authors extracted the year of publication, study period, country, the definition of subacute cough, sample size, type and duration of intervention and control treatment, and duration of follow-up. They extracted any health outcomes and the timepoints of their measurement. They sent multiple emails to the corresponding authors of the included studies and asked for additional outcome data (cough scores for 14 days and 28 days). However, the authors obtained no further pertinent data.

All data were independently extracted by two authors. Disagreements were resolved by discussion with a third author. Two authors independently assessed the risk of bias, following Cochrane standards.[19] Disagreements were resolved by discussion.

Statistical analysis

The authors evaluated all individual study results separately. They also conducted a meta-analysis to assess if treating subacute cough with any treatment is more favourable overall than no treatment. The authors quantitatively synthesised the effects on cough scores at the same timepoints using random effects meta-analyses (they used fixed effects for sensitivity analyses). The authors used standardised mean differences (SMD) due to the diversity of cough scores and applied the Hedges' g[24] method (using the metacont function of the meta-package, www.r-project.org).[25] The authors synthesised only results for cough scores because they were the only reported clinically comparable outcomes. They investigated the natural disease progression descriptively and by synthesising cough scores in control groups for the same timepoints.

RESULTS

Results of the search

The electronic search yielded 691 publications (Figure 1). Six RCTs were eligible (Table 1).[26–31] The studies were typically small, including between 30 and 276 patients (median 96, interquartile range [IQR] 76–170), and were

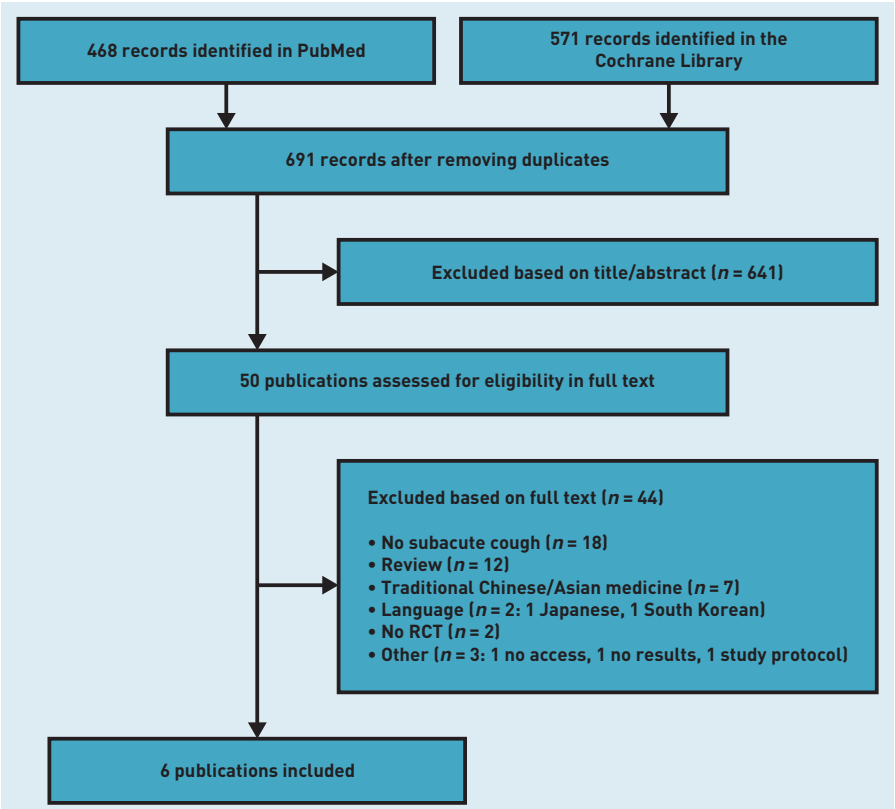

Figure 1. Study selection. RCT = randomised controlled trial.

conducted between 2000 and 2012 in the UK,[26] Italy,[27] Netherlands,[30] Thailand,[31] Iran,[29] or multicentrically (that is, Europe, South America, and Africa).[28] They explored effects of orally administered montelukast,[26] inhaled salbutamol plus ipratropium bromide,[27] oral gelatine,[29] inhaled fluticasone propionate,[30] and inhaled budesonide[31] (Table 1). One study had three study arms investigating an orally active selective nociception opioid 1 (NOP1) receptor agonist and oral codeine.[28] The comparator was placebo in five studies, and continued usual care in one.

With the exception of Zanasi[27] all studies included some patients with acute or chronic cough (17% to 33%, when stated) but did not report effects for subacute cough (3–8 weeks) separately (Table1).

Risk of bias assessment

Five studies blinded patients and care providers, or were reported as double blind.[26–28,30] Wang[26] and Pornsuriyasak[31] also reported blinded outcome assessment. Zanasi was deemed to have a substantial risk of bias because patients with symptom increase or indications of harm (adverse events) were excluded from analyses.[27] Overall, the risk of bias was often unclear due to poor reporting in several studies (Table 2).

Outcomes

Cough severity score changes between baseline and different timepoints were reported for five studies.[26–28,30,31] They were the primary outcome in Wang,[26] Zanasi,[27] Woodcock,[28] and Ponsioen.[30] In Pornsuriyasak[31] this was the only outcome with detailed results (Table 1). Wang used the Leicester Cough Score (as a measure of the cough-specific quality of life). Further endpoints were often not reported transparently and included types of cough-related outcomes, lung function, adverse effects, and various other outcomes typically recorded in patient diaries (including sleep affection, absence from work, and perception of improvement). No study reported general effects on health-related quality of life (beyond the cough-specific quality of life), hospitalisations, or mortality.

Cough severity score

Five studies reported on cough severity scores at various timepoints (Table 3).[26–28,30,31] No treatment was associated with a clear clinically relevant improvement of cough scores. Two studies reported possible indications for beneficial treatment effects compared to placebo: Ponsioen[30] reported a favourable effect of inhaled fluticasone over 14 days measured on an unspecified cough score (without any details about validation) ranging on a scale from 0–6. The researchers found a statistically significant improvement under fluticasone in the total trial population (including 64% non-smokers) of 0.5 points (95% confidence interval [CI] = 0.1 to 0.9) compared to placebo after 2 weeks. There was a statistically significant subgroup effect for smoking status (prespecified subgroup), showing an improvement only in non-smoking patients (cough score 0.9 points lower than with placebo, 95% CI = 0.4 to 1.3), but not in smokers (0.1 points, 95% CI = –0.6 to 0.9). This effect was of a similar magnitude to the baseline standard deviation among all patients (1.0 points), and was described as 'could be clinically relevant'.[30] However, one-third of included patients had acute cough (<3 weeks, 23%) or chronic cough (8–17 weeks, 10%). There were no separate results for subacute cough. The other trial that evaluated inhaled steroids (Pornsuriyasak[31]) found no benefit on cough outcomes at all (Table 3).

Zanasi reported more favourable effects on cough severity after 10 days of treatment with salbutamol plus ipratropium bromide which was not sustained beyond 20 days.[27]

The meta-analyses combining effects of the three studies that assessed cough scores 14 days after treatment initiation

Table 1. Characteristics of randomised clinical trials assessing different treatment for subacute cough

Publication	Year conducted	Country	Number of patients	Cough duration	Number of patients with subacute cough	Intervention(s) and control Duration of follow-up	Duration of treatment of measurement, days	Primary outcome and time-point	Other outcomes
Wang *et al*, 2014[26]	2011–2012	UK	276	2–8 weeks	NR[a]	Montelukast 10 mg daily versus placebo	14[b] 28	LCQ score (cough specific quality of life) at day 14 and 28	• Overall cough severity • Paroxysms of cough • Cough cessation • Cessation of exercise-induced cough • Further interventions for cough • Adverse events
Zanasi *et al*, 2014[27]	2011–2012	Italy	92	≥3 weeks and <4 weeks after URTI	92 (100%)	Salbutamol 1.875 mg/0.5 ml plus ipratropium bromide 0.375 mg/0.5 ml versus placebo	10 20	Cough severity (daytime and night-time separately) at day 10 or 20[c]	• Lung function • Adverse events
Woodcock *et al*, 2010[28]	NR	UK, Latin America, South Africa	91	≥2 weeks and ≤90 days after viral URTI	NR[d]	NOP1 receptor agonist 100 mg twice daily versus codeine 30 mg twice daily versus placebo	5 5	Cough severity at day 5	• Cough frequency • Stanford sleepiness scores • Patient diary[e] • Adverse events
Zolghadrasli, 2009[29]	2006–2007	Iran	100	>3 weeks	83 (83%)[f]	Gelatine 5 cc (a teaspoon) three times a day versus continuation of the previous antitussive medication	3–5 6–10	NR	• 'Subjective assessment of improvement' • Adverse events
Ponsioen *et al*, 2005[30]	2000–2001	Netherlands	135 (89 subacute cough 3–8 weeks)	≥2 weeks[g]	89 (67%)[g]	500 µg inhaled fluticasone propionate twice daily versus placebo	14 14	Cough score (daytime) at 14 days	• Cough score improvement >50% • Perception of improvement • Additional treatment required after 14 days • Days off work • Lung function • Patient diary[h] • Adverse events
Pornsuriyasak *et al*, 2005[31]	NR	Thailand	30	>3 weeks	NR[i]	Four puffs of 100 µg budesonide twice daily versus placebo	28 28	NR	• Symptom score (at 14 and 28 days) • Lung function

[a]Mean duration 5 weeks (SD 1.9) in the intervention and 4.8 weeks (SD 1.8) in the control group, with 48% of patients ≤4 weeks. No subgroup for subacute cough (3–8 weeks) reported. [b]Participants could choose to continue treatment. [c]Reporting not clear. [d]Persistent cough described as subacute cough after a viral upper respiratory tract infection lasting 14–90 days. Median cough duration of 33 days, range 16–99 days. No subgroup for subacute cough (3–8 weeks) reported. [e]Including cough frequency, lack of sleep, interference with daytime activity, and a general question on how the cough has affected the patient. No results are reported beyond stating that there were 'no significant differences'. [f]Included 17 of 100 patients (17%) with cough lasting >8 weeks. No subgroup for subacute cough (3–8 weeks) reported. [g]Included 31 of 133 patients (23%) with cough lasting 2–3 weeks and 13 patients (10%) with cough lasting >8 weeks. No subgroup for subacute cough (3–8 weeks) reported. [h]Including cough, sputum production, wheezing, shortness of breath, chest tightness, number of awakenings, number of cigarettes smoked. [i]Included patients with cough lasting >3 weeks and only presents the mean cough duration at baseline (treatment group: 5.93 weeks, SD 1.94; control group: 4.66 weeks, SD 2.05). No subgroup for subacute cough (3–8 weeks) reported. [j]Included in meta-analysis.
LCQ = Leicester Cough Questionnaire. NOP1 = nociception opioid 1. NR = not reported. SD = standard deviation. URTI = upper respiratory tract infection. VCD = verbal category descriptive.

Table 2. Risk of bias summary of the included studies

	Random sequence generation	Allocation concealment	Blinding of patients and personnel	Blinding of outcome assessment	Analysed as randomised	Attrition bias and missing data (>10%)
Wang, 2014[26]	+	+	+	+	+	–[a]
Zanasi, 2014[27]	+	?	+[b]	?[b]	+	–[c]
Woodcock, 2010[28]	?	?	+[b]	?[b]	+	(+)[d]
Zolghadrasli, 2009[29]	?	?	–	–	?	+
Ponsioen, 2005[30]	+	+	+[b]	?[b]	+	+
Pornsuriyasak, 2005[31]	?	?	+	+	?	(–)[e]

[a]<80% of patients with outcome data at week 4 (co-primary outcome). For 2 weeks (co-primary outcome), 87% of patients with primary outcome data. [b]Study placebo-controlled and reported as double-blind. The authors think it is likely that patients and personnel conducting the intervention were blinded, but this is unclear for the outcome assessor and the outcomes are subjective. [c]Of 92 randomised patients, nine were excluded from the analysis due to adverse events (n = 5) or 'increased cough' (n = 4). [d]For the primary outcome (cough severity scores), only two of 91 randomised patients dropped out. In 17 out of 91 patients there were technical problems with the device used for objectively monitoring cough (secondary outcomes). [e]For the 2-week cough score results, data for all 30 randomised patients were available. For the 4-week timepoint, three of 15 randomised patients in the control group (20%) had no data assessment (one of 15 in the experimental treatment group, 7.5%). Green = low risk of bias. Pink = high risk of bias. Yellow = unclear risk of bias.

(Wang,[26] Ponsioen,[30] Pornsuriyasak[31]), and of two studies assessing after 28 days (Wang,[26] Pornsuriyasak[31]) (Figure 2), showed no benefit (14 days: SMD –0.12, 95% CI = –0.46 to 0.21), and 28 days (28 days SMD –0.01, 95% CI = –0.24 to 0.21). The sensitivity analyses using fixed effect models showed similar results (14 days: SMD –0.08, 95% CI = –0.27 to 0.11. 28 days: SMD –0.01, 95% CI = –0.24 to 0.21). Between-study heterogeneity was substantial (14 days I^2: 56%, 95% CI = 0% to 87%), or not meaningful with only two studies (28 days I^2: 0%).[25]

Overall, cough improved with and without treatment in all studies. In the largest trial (Wang[26]), the improvement under placebo over 14 days and 28 days (score change 3.6, 95% CI = 2.9 to 4.3, and 5.9, 95% CI = 5.1 to 6.7) was above the described minimal clinically important difference of 1.3 (Table 4). The meta-analytically combined improvements of cough at 14 and 28 days were similar or even stronger (further details available from the authors on request).

Other cough-related outcomes

Four studies reported other cough-related outcomes with various levels of details (Table 1).[26,28–30]

Wang found no relevant effect of monelukast on overall cough severity, paroxysmal cough severity, the likelihood of cough cessation, and cessation of exercise-induced cough, and similar rates of patients received further treatments.[26]

Woodcock found no association of treatment with a NOP1 agonist or with codeine on cough frequency when compared to placebo.[28]

Ponsioen reported dichotomised success rates (>50% reduction of mean cough scores) of 80.4% (33 of 41 patients) for non-smokers treated with inhaled fluticasone versus 54% (23 of 43 patients) given placebo. They

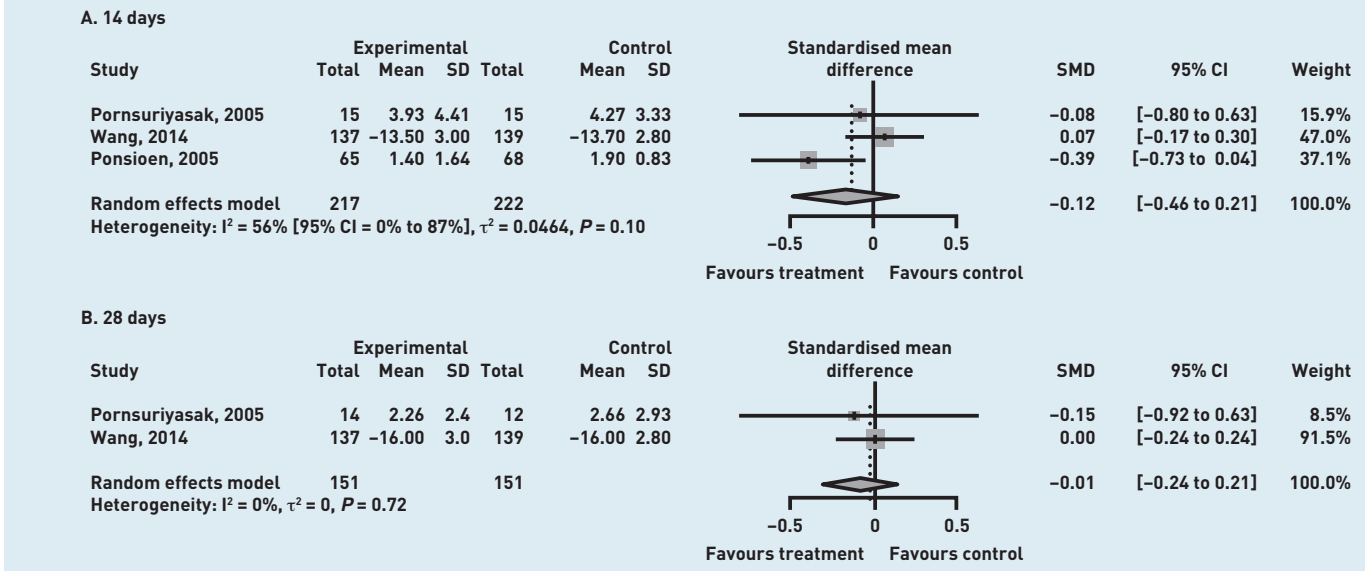

Figure 2. Treatment effects on cough scores after 14 days(A), and 28 days (B). SD = standard deviation. SMD = standard mean difference.

The score used in Wang, 2014 has a different direction, that is, scores >0 meant a better cough score, while in the other studies it was the other way around. Therefore, to unify the direction of the scores, the authors multiplied the mean of Wang, 2014 by –1.

Table 3. Five randomised controlled trials reporting cough severity scores at different timepoints

Publication	Treatment comparison	Time point, days	Patients analysed/ randomised	Outcome definition	Experimental mean (95% CI)	Control mean (95% CI)	Group difference mean (95% CI)
Wang *et al*, 2014[26]	Montelukast versus placebo	14	Exp: 137[a]/137 Ctrl: 139[a]/139	Change in the LCQ between baseline and two follow-up stages	2.7 (2.2 to 3.3)[b]	3.6 (2.9 to 4.3)[b]	–0.9 (–1.7 to –0.04)[c,d]
		28	Exp: 137[a]/137 Ctrl: 139[a]/139		5.2 (4.5 to 5.9)[b]	5.9 (5.1 to 6.7)[b]	–0.5 (–1.5 to 0.6)[c,d]
Zanasi *et al*, 2014[27]	Salbutamol plus ipratropium bromide versus placebo	10	Exp: 41/46 Ctrl: 42/46	The change in both daytime and night time cough severity, as assessed by the verbal category descriptive score	Daytime: 1.32 (0.93 to 1.71)[e] Night time: 0.37 (0.17 to 0.57)[e]	Daytime: 2.14 (1.73 to 2.55)[e] Night time: 0.74 (0.49 to 0.99)[e]	NR
		20	Exp: 41/46 Ctrl: 42/46		Daytime: 0.41 (0.17 to 0.65)[e] Night time: 0.15 (0.02 to 0.28)[e]	Daytime: 0.64 (0.38 to 0.90)[e] Night time: 0.17 (0.04 to 0.30)[e]	NR
Woodcock *et al*, 2010(A)[28]	NOP1 receptor agonist versus placebo	5	Exp: 26/27 Ctrl: 30/30	Change in cough severity scores	–0.57 (NR)	–0.49 (NR)	NR
Woodcock *et al*, 2010(B)[28,f]	Codeine versus placebo	5	Exp: 33/34 Ctrl: 30/30		–0.72 (NR)	–0.49 (NR)	NR
Ponsioen *et al*, 2005[30]	Fluticasone propionate versus placebo	14	Exp: 65/67 Ctrl: 68/68	Cough score	1.4 (0.2 SEM)	1.9 (0.1 SEM)	NR
Pornsuriyasak *et al*, 2005[31]	Budesonide versus placebo	14	Exp: 15/15 Ctrl: 15/15	Symptom score	3.93 (1.70 to 6.16)[e]	4.27 (2.58 to 5.96)[e]	NR
		28	Exp: 14/15 Ctrl: 12/15		2.26 (1.00 to 3.52)[e]	2.66 (1.00 to 4.32)[e]	NR

[a]Missing data imputed by study authors using last observation carried forward: 14 days: 19 (Exp) and 17 (Ctrl). 28 days: 26 (Exp) and 29 (Ctrl). [b]Mean difference in scores compared to baseline. [c]Adjusted for numerous baseline variables (baseline scores, age, sex, duration of cough, pertussis status, pertussis immunisation status, atopy, paroxysmal cough severity, and exercise-induced cough severity); unadjusted analysis slightly and not relevantly different. Higher LCQ score indicates higher quality of life. Therefore the result is in favour of the control. [d]Higher Leicester Cough Questionnaire score indicates higher quality of life, that is, the result is in favour of the control. For all other cough scores, lower values indicate fewer cough symptoms. [e]95% CI calculated by authors from standard deviation. [f]Woodcock A and B refers to the randomised controlled trial (reference 28) which consists of three treatment arms. The first line in Table above lists the NOP1 receptor agonist versus placebo and the second describes codeine versus placebo. Ctrl = control group. Exp = experimental group. LCQ = Leicester Cough Questionnaire. NOP1 = nociception opioid 1. NR = not reported. SEM = standard error of the mean.

also observed fewer requests for additional treatment after 14 days of fluticasone compared to placebo (28 of 65 patients, 43%, versus 42 of 67 patients, 63%).[30]

The patient's perception of cough improvement was reported in Zolghadrasli, who categorised self-reported response into 'no', 'poor', 'fair', 'good', and 'excellent' (without further details of operationalisation), and described an overall better response with oral gelatine.[29] Ponsioen made a statement that was not further specified that after 14 days patients perceived themselves to be 'significantly better' following treatment with fluticasone.[30]

Lung function

Three studies assessed the lung function of patients with overall scarce data.[27,30,31] Zanasi reported results for eight spirometric comparisons of ipratropium plus salbutamol versus placebo over follow-up (showing nominally statistically significant differences in one case for forced expiratory volume in 1 second [FEV1] after 10 days).[27]

Both Ponsioen and Pornsuriyasak stated that there were no statistically significant differences in spirometric parameters (without providing specific outcome data).[30,31]

Adverse events

Five studies reported adverse events.[26–30] Across all studies and treatments, adverse events were reported for 98 of 694 analysed patients (14% of patients across all study arms), with absolute rates ranging from 0% to 40% across experimental treatment groups, and 0% to 27% across control groups. Adverse events were typically described as rather mild symptoms (mucus production, nasal symptoms, dry mouth, chest or breast discomfort, fainting, headache, nausea, general gastrointestinal complaints, hoarseness, sore throat, and oropharyngeal candidiasis). No study reported serious adverse events specifically.

Table 4. Improvement of cough over time with no treatment (placebo)

Publication	Control Treatment	Time point, days	Patients analysed	Outcome definition	Baseline, mean (95% CI)	Follow-up, mean (95% CI)	Change from baseline (95% CI)	MID
Wang *et al*, 2014[26]	Placebo	14	Baseline: 139 Follow-up: 139[a]	Change in the Leicester Cough Questionnaire	10.10 (9.6 to 10.6)[b]	NR	3.6 (2.9 to 4.3)[c]	1.3
		28	Baseline: 139 Follow-up: 139[a]		10.10 (9.64 to 10.57)[b]	NR	5.9 (5.1 to 6.7)[c]	1.3
Zanasi *et al*, 2014[27]	Placebo	10	Baseline: 46 Follow-up: 42	The change in both daytime and nighttime cough severity	Daytime: 3.49 (3.28 to 3.70)[b,d] Nighttime: 1.38 (0.99 to 1.77)[b,d]	Daytime: 2.14 (1.73 to 2.55)[b] Nighttime: 0.74 (0.49 to 0.99)[b]	NR	NR
		20	Baseline: 46 Follow-up: 42		Daytime: 3.49 (3.28 to 3.70)[b,d] Nighttime: 1.38 (0.99 to 1.77)[b,d]	Daytime: 0.64 (0.38 to 0.90)[b] Nighttime: 0.17 (0.04 to 0.30)[b]	NR	NR
Woodcock *et al*, 2010[28]	Placebo	5	Baseline: 30 Follow-up: 30	Change in cough severity scores	2.01 (NR)	1.52 (NR)	-0.49 (NR)	NR
Ponsioen *et al*, 2005[30]	Placebo	14	Baseline: 68 Follow-up: 68	Cough score	3.8 (3.56 to 4.04)[b]	1.9 (NR; SEM 0.1)	NR	NR
Pornsuriyasak *et al*, 2005[31]	Placebo	14	Baseline: 15 Follow-up: 15	Symptom score	9.8 (8.59 to 11.02)[b]	4.27 (2.58 to 5.96)[b]	NR	NR
		28	Baseline: 15 Follow-up: 12		9.8 (8.59 to 11.02)[b]	2.66 (1.00 to 4.32)[b]	NR	NR

[a]Missing data imputed by study authors using last observation carried forward: 14 days: 17; 28 days: 29. [b]95% CI calculated by us from standard deviation. [c]Higher Leicester Cough Questionnaire score indicates higher quality of life; that is, the result is in favour of the control. For all other cough scores lower values indicate fewer cough symptoms. [d]Values extracted from figure. MID = minimally important difference. NR = not reported. SEM = standard error of mean.

Other outcomes

Information on other outcomes was scarce and not reported transparently. Ponsioen found no impact of fluticasone on days off work, nocturnal awakenings, and lower respiratory tract symptoms, but they reported lower sputum scores (not further specified) after 14 days compared to placebo.[30] Woodcock stated that there was no patient-reported impact on sleep or daytime activities but a 'nonsignificant trend' for higher Stanford sleepiness scores in patients who received NOP1 receptor agonist.[28]

DISCUSSION

Summary

This systematic review included six RCTs assessing the benefits and harms of seven different treatment regimens for subacute cough. The treatments, settings, outcomes, and durations of follow-up were highly heterogeneous. The reporting quality was frequently poor and limited the risk of bias assessment. Overall, there was no clear benefit associated with any of these treatments, even though two studies found some indications for favourable effects.

One trial (Ponsioen),[30] indicated a beneficial effect of inhaled steroids on cough recovery in the overall study population, which was explained by beneficial effects in the subgroup of non-smokers, but this trial included many patients without subacute cough. The other trial with potential indications of benefits (Zanasi),[27] found a difference with salbutamol plus ipratropium bromide compared to placebo on cough severity scores 10 days after randomisation, but not after 20 days. These findings, however, were based on an analysis excluding 10% of patients with 'increased cough' or adverse events.

Strengths and limitations

Various limitations merit closer attention. First, the authors only searched PubMed/MEDLINE and the Cochrane Central Register of Controlled Trials and, therefore, might have missed trials published in journals which are not indexed in these databases. However, the authors also screened reference lists, systematic reviews, and treatment guidelines without identifying further pertinent studies. Second, although the authors considered English, German, Italian, Spanish, and French literature, they excluded two articles in Asian languages (one Japanese, one South Korean). They also did not consider Chinese or Asian herbal medicine, often assessed in numerous RCTs published in

Chinese, South Korean, or Japanese.[32–36] The inclusion of these treatment options would have been beyond the scope of this project, which aimed to summarise the evidence for treatments that are commonly used by GPs and their patients in Europe and North America. Third, four of the six articles that were included had a high risk of bias in at least one domain, and the risk of bias was often unclear due to poor reporting. Fourth, with one exception, all RCTs included some patients with shorter or longer cough duration (then defined as acute or chronic cough), and did not report separate treatment effects for patients with a cough duration of 3–8 weeks. Hence, the generalisability may be limited. Fifth, the authors did not assess publication bias due to the limited number of studies.[19] Sixth, improvement of cough severity as the most commonly assessed outcome was measured with cough scores that were different across trials (or it was unknown which specific score was used), and the timepoints of their measurement was highly heterogeneous between trials. Finally, many other cough-related outcomes were poorly reported, often stating that no significant difference was detected without specifying the effect size.

Comparison with existing literature

These results are similar to those of a 2014 Cochrane Review of inhaled corticosteroids for acute cough, which concluded that 'there is no good evidence for or against over-the-counter medicines in acute cough'.[37] A 2013 Cochrane Review and a systematic review by El-Gohary *et al* evaluated inhaled corticosteroids for subacute and chronic cough,[16] as well as for acute and subacute cough.[17] Both reviews identified the same two studies[30,31] for subacute cough that the authors of this current review found, and the articles similarly conclude that *'… the data were too mixed to be able to draw any conclusions'*,[16] and that there is *'… insufficient evidence to recommend the routine use of inhaled corticosteroids'*.[17] Remarkably, antitussive agents that are currently used in clinical practice were developed several decades ago and there has been little progress in the meantime, although the need for effective antitussive treatments seems obvious.[8] This systematic review identified no RCTs for other potential treatment options, such as oral corticosteroids, which are efficient against asthma and COPD in cases where the cough is also mediated by inflammatory processes, as in subacute cough.[38–40]

Implications for practice

Overall, this systematic review clearly emphasises the limited available evidence on therapeutic options for subacute cough. However, it also shows that the symptoms diminish over time as a natural course of the self-limiting disease. Therefore, considering the problem of overtreatment,[41,42] spending time with the patient to explain the illness might be crucial for patient satisfaction.[43]

This review indicates that, despite being one of the most common causes for seeking medical advice in primary care, there is no beneficial treatment for subacute cough.

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